Acute Coronary Syndromes

AMPLIFICATION OF THE MYOCARDIAL INFARCT SIZE LIMITING EFFECTS OF EXENATIDE WITH CILOSTAZOL, A PHOSPHODIESTERASE III INHIBITOR

ACC Moderated Poster Contributions
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Background: Glucagon-like Peptide (GLP1) analogues reduce myocardial infarct size (IS) in nondiabetic animals. Ischemic and pharmacological preconditioning of diabetic animals is limited. Activation of the GLP1 receptors increases intracellular cAMP with downstream activation of protein kinase A (PKA). Cilostazol (CIL), a phosphodiesterase III inhibitor prevents the degradation of cAMP and augments the IS-limiting effects of statins. We assessed whether CIL augments the IS-limiting effects of exenatide (EX), a GLP1 analogue, by increasing intracellular cAMP in mice with type-2 diabetes mellitus.

Methods: Db/Db mice fed a Western Diet received oral CIL (10 mg/kg) or vehicle by oral gavage 24h before surgery. One hour before surgery mice received S.C. EX (1 mcg/kg) or vehicle. Additional mice received H89, a PKA inhibitor, alone or with CIL+EX. Mice were subjected to 30 min coronary artery occlusion and 24h reperfusion. Ischemic area at risk (AR) was assessed by blue dye and IS by TTC.

Results: Body weight, left ventricular weight and the size of the AR were comparable among groups. Both EX and CIL reduced IS. IS was the smallest in the CIL+EX group (Figure). IS in the H89 group was 48.2±4.6% of the AR and in the CIL+EX+H89 45.8±1.4% (p=.117). Both EX and CIL increased cAMP. cAMP levels were significantly higher in the CIL+EX group.

Conclusion: EX and CIL have additive IS-limiting effects in diabetic mice. The additive effects are related to cAMP induced PKA activation, as H89 blocked the effect of CIL+EX.